UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: February 11, 2019

SUBJECT: Sulfometuron Methyl: Summary of the Hazard and Science Policy Council (HASPOC) Meeting of August 23, 2018: Recommendations on the Requirement of Rat Developmental, Reproduction Toxicity, and Rat Chronic/Carcinogenicity Studies.

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Petition No.: N/A	**Regulatory Action:** N/A
Risk Assessment Type: N/A	**Case No.:** N/A
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MRID No.: N/A	**40 CFR:** N/A

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MEETING ATTENDEES:

HASPOC Members: Elissa Reaves, Elizabeth Mendez, Angela Gonzalez, Jonathan Chen, Matt Crowley, Michael Metzger, P.V. Shah, Kristin Rickard [#], Chris Schlosser, Anwar Dunbar, Evisabel Craig [#], Connor Williams [*], Krystle Yozzo [*]

#: HASPOC Chairs, *: HASPOC Executive Secretaries

Presenters: Monique Perron

Other Attendees: None

I. PURPOSE OF MEETING:

A petition has been submitted by DuPont to establish tolerances without U.S. registration for sulfometuron methyl in/on sugarcane commodities. This is the first food use for this chemical. The toxicology database for sulfometuron methyl is complete except for rat developmental, reproduction toxicity, and rat carcinogenicity studies that are required in accordance with the current 40 CFR Part 158 Toxicology Data Requirements. The Hazard and Science Policy Council (HASPOC) met on August 23, 2018 to discuss the need for these studies to support the new food use action.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Sulfometuron methyl [methyl 2-[[[[(4,6-dimethyl-2-pyrimidinyl)amino]carbonyl]amino] sulfonyl]benzoate], is a sulfonylurea (SU) herbicide that provides broad spectrum pre- and postemergence control of annual and perennial grasses and broad-leaf weeds in forestry/Christmas trees and non-agricultural situations, including vegetative management of rights-of-way and railroads. Similar to other SU herbicides, sulfometuron methyl's pesticidal mode of action involves inhibiting the activity of the enzyme acetolactate synthase (ALS), which inhibits the production of amino acids required for cell growth in plants.

All sulfometuron methyl-containing products currently registered in the U.S. are formulated as water dispersible granules (WDGs). Applications of sulfometuron methyl can be made aerially by fixed-wing airplane and helicopter, and by groundboom or hand-held equipment. Additionally, sulfometuron methyl can be used to impregnate or coat dry bulk fertilizer for application to forested areas. Personal protective equipment (PPE) recommended on registered labels typically includes long sleeve shirts, long pants, and socks, with some labels also recommending the use of chemical resistant gloves and protective eyewear.

The last human health risk assessment for sulfometuron methyl was conducted to support Registration Review (K. Lowe; 15-SEP-2015; D427028). An acute dietary endpoint was not selected because effects attributable to a single dose were not identified. The chronic oral toxicity study in dogs was used to evaluate chronic dietary, incidental oral, dermal, and inhalation exposures. The no observed adverse effect level (NOAEL) of 27.5 mg/kg/day was based on decreases in body weight gain, hemolytic anemia, and a slight increase in alkaline phosphatase at the lowest observed adverse effect level (LOAEL) of 148.5 mg/kg/day. A dermal

absorption factor (DAF) of 100% was applied to evaluate dermal exposures. Inhalation exposure was assumed to be equivalent to oral exposure. Uncertainty factors for interspecies extrapolation (10X) and intraspecies variability (10X) were applied to all scenarios. It should be noted that most of the studies in the SU toxicological databases, including those used for endpoint selection, have not been updated to reflect current policies and practices in hazard assessment and may be considered conservative. Given the current risk picture, any updates are not expected to impact the overall findings of the sulfometuron methyl risk assessment because these updates would result in higher NOAEL/LOAEL values.

In previous assessments, dietary exposure consisted of drinking water only since there were no food uses. A high-end drinking water exposure value for SUs was used to assess dietary exposure in the last human health risk assessment. Chronic dietary risk estimates were <10% of the chronic reference dose (cRfD) for all subpopulations. The new petition received from DuPont to establish tolerances without U.S. registration for sulfometuron methyl in/on sugarcane commodities will be the first food use for this chemical and, therefore, the new tolerances will be incorporated into the dietary assessment. With inclusion of the proposed new tolerances, the dietary risk estimates remain <10%. There are no currently registered or proposed residential uses for sulfometuron methyl. Exposure in non-occupational settings from spray drift was evaluated as part of Registration Review for the currently registered uses. Margins of exposure (MOEs) at the edge of the field ranged from 500-1,400 (level of concern (LOC) for MOEs <100) using screening-level droplet sizes, boom heights, default turf transferrable residue estimates, and maximum registered application rates. Short- and intermediate-term occupational exposures are expected only from the currently registered uses of sulfometuron methyl. For all scenarios, combined dermal and inhalation risk estimates for handlers were not of concern (i.e., MOEs ≥100) with either baseline protection or label-specified PPE (MOEs ranged from 110 to 11,000. Occupational post-application dermal exposures are also only expected from the currently registered uses and were not of concern on the day of treatment for all scenarios (MOEs ranged from 260-20,000).

III. STUDY WAIVER REQUESTS:

a. Rat Developmental Toxicity Study

A prenatal developmental toxicity study in rats is required for a food use chemical according to the 40 CFR Part 158 Toxicology Data Requirements. The currently available rat developmental toxicity study for sulfometuron methyl (MRID 00078796) was classified as unacceptable because only summary data was submitted and no individual animal data were provided, test groups were a combination of three non-concurrently run studies, no rationale was provided to support dietary administration of the test material, environmental conditions were not reported, and homogeneity/stability/concentration analyses were not performed (L. Chitlik; 6-FEB-2008; D345341, D345421, D345458, D345302; TXR 0054522).

1. **Evidence for developmental toxicity in the database:** A rabbit developmental toxicity study is available for sulfometuron methyl (MRID 00078798). The LOAEL is 750 mg/kg/day based on abortions observed in 2 does in the range-finding study (NOAEL = 300 mg/kg/day.

2. **Evidence for developmental toxicity in the database for structurally similar chemicals:** There are 22 other SU chemicals registered, which all contain a central SU structure that terminates in different structures depending on the SU (Figure 1). Of these, 13 are pyrimidinyl SU chemicals, like sulfometuron methyl, that contain a pyrimidine substituent on the urea side of the molecule (R_2). The other 9 are triazinyl SU chemicals, which contain a triazine ring substituent.

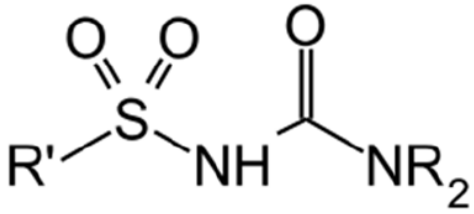

Figure 1. Sulfonylurea chemical structure

Qualitative or quantitative susceptibility was not commonly observed in the SU database. When there was susceptibility in offspring, it was of low concern because there were clearly established NOAELs and the endpoints chosen for risk assessment were protective of the developmental effects.

For 18 of the other SUs registered, either developmental effects were not observed up to the limit dose (1000 mg/kg/day) or developmental effects were only observed at doses approaching or exceeding the limit dose in the rat developmental toxicity studies. For the remaining 4 chemicals (2 pyrimidinyl and 2 trazinyl SUs), developmental effects were seen at doses ≥ 125 mg/kg/day and the NOAEL/LOAEL values for the rat developmental were similar to those for the rabbit. Furthermore, the chronic oral toxicity study in dogs, which is the study used to establish points of departure (PODs) for sulfometuron methyl, provided lower NOAEL/LOAEL values than the rat developmental toxicity studies. Only 2 SUs use the rat developmental toxicity study to set endpoints for risk assessment (dermal exposures for primisulfuron methyl and acute dietary for thifensulfuron methyl). In both cases, the developmental effects were seen only at a relatively high dose (≥500 mg/kg/day). Additionally, the effects in the thifensulfuron methyl study (3% decrease in fetal body weight and a slight increase in the incidence of small renal papillae) would not be considered an acute effect under current practices in hazard evaluation.

In the rabbit developmental studies, developmental effects were not observed or were only observed at relatively high doses (≥500 mg/kg/day) for 15 of the other SUs registered. For the remaining 7 chemicals, the rabbit developmental toxicity study provided similar or lower NOAEL/LOAEL values as the rat developmental toxicity study. Similar to the rat developmental toxicity study, the chronic oral toxicity study in dogs for each SU provided similar or lower NOAEL/LOAEL values as the rabbit developmental toxicity study.

3. **Risk assessment considerations:** In the last risk assessment (K. Lowe; 15-SEP-2015; D427028), the chronic dietary risk estimates were <10% of the cRfD for all subpopulations using a high-end drinking water exposure value for SUs. With the addition of the tolerances in/on sugarcane commodities, chronic dietary risk estimates are still <10% of the chronic population adjusted dose (cPAD). As discussed above, non-occupational spray drift and occupational handler and post-application risk estimates were not of concern (i.e., MOEs ≥100). Dermal assessments are also considered conservative since a DAF of 100% was applied to evaluate dermal exposures. Inhalation exposure was assumed to be equivalent to oral exposure. The proposed use for tolerances without U.S. registrations will not result in any changes to the risk estimates calculated for domestic uses.

Based on a weight of evidence (WOE) approach, the HASPOC recommends that the developmental toxicity study in rat is not required for sulfometuron methyl at this time. This approach was based on the following considerations (1) a rabbit developmental toxicity study is available where effects were only seen at 750 mg/kg/day; 2) developmental effects for the SUs, including the rabbit developmental study for sulfometuron methyl, are generally seen at relatively high doses; (3) the rabbit developmental study provides similar or lower NOAEL/LOAEL values as the rat developmental toxicity study for the currently registered SUs; (4) the rat developmental study has only been used to set endpoints for SU risk assessments in limited instances; (5) the chronic oral toxicity study in dogs, which is the study used to establish PODs for sulfometuron methyl, provides lower NOAEL/LOAEL values than the rat developmental toxicity study for each SU; and (6) including the proposed new tolerances, dietary risk estimates are <10% of the cPAD using a high-end drinking water exposure value for SUs and there would be no impact on risk estimates calculated for domestic uses.

b. Reproduction Toxicity Study

A reproduction toxicity study in rats is required for a food use chemical according to the 40 CFR Part 158 Toxicology Data Requirements. A combined chronic toxicity/oncogenicity and two-generation reproduction study was previously submitted to the Agency (MRID 42385705), which consisted of a 2-year chronic toxicity/oncogenicity study with a concurrent two-generation reproduction toxicity substudy. Animals were dosed at 0, 50, 500, or 5000 ppm (equivalent to 0, 3, 34, or 337 in males and 0, 4, 44, and 424 in females, respectively). Treatment-related effects were limited to the high-dose and consisted of slight decreases in female body weight (~5%) and decreased litter size (R. Fricke; 23-FEB-1993; D185389; TXR 0054624). The Agency concluded that this study was core-supplementary and did not satisfy the guideline requirement for a reproduction toxicity study. Animal body weights and food consumption were not measured during gestation and lactation. Furthermore, gross necropsies and histopathological evaluations were not performed on parental animals. While this study does not meet all of the requirements of the EPA's guideline, the registrant has provided an argument for this study to be considered sufficient for evaluation of potential impacts on reproductive function and performance to support the proposed tolerances without U.S. registration in/on sugarcane commodities (MRID 50034007). This argument included the following considerations:

1. The existing data in the study gives no indication of an impairment of reproduction, except for a possible spurious finding. While a decrease in litter size was reported at the

highest dose tested, it was only statistically significant for one of the four pairings (F_{2B} generation).

2. The low probability of an effect on reproduction to drive the risk assessment based on this class of chemistry. The registrant reviewed the recent risk assessments for the 13 pyrimidinyl SU chemicals and found that the rat reproduction toxicity study was not used to set any dietary PODs. The most common findings in the reproduction toxicity studies were signs of parental toxicity related to decreases in body weight.
3. The negligible residue expected in the imported commodity.

Furthermore, the chronic oral toxicity study in dogs, which is the study used to establish PODs for sulfometuron methyl, provided similar or lower NOAEL/LOAEL values as the reproduction toxicity study for the other registered SUs, except for one SU chemical (metsulfuron) where the only effect observed was decreased body weight in parental animals at the highest dose tested (342 and 475 mg/kg/day in males and females, respectively) and there were no effects in the chronic dog study; however, it only tested up to 125 mg/kg/day.

In the last risk assessment (K. Lowe; 15-SEP-2015; D427028), the chronic dietary risk estimates were <10% of the cRfD for all subpopulations using a high-end drinking water exposure value for SUs. With the addition of the tolerances in/on sugarcane commodities, chronic dietary risk estimates are still <10% of the cPAD. As discussed above, non-occupational spray drift and occupational handler and post-application risk estimates were not of concern (i.e., MOEs ≥100). Dermal assessments are also considered conservative since a DAF of 100% was applied to evaluate dermal exposures. Inhalation exposure was assumed to be equivalent to oral exposure. The proposed use for tolerances without U.S. registrations will not result in any changes to the risk estimates calculated for domestic uses.

Based on a weight of evidence (WOE) approach, the HASPOC recommends that the reproduction toxicity study in rats is not required for sulfometuron methyl at this time. This approach was based on the following considerations (1) the core-supplementary study only observed effects at the highest dose tested (337 and 424 mg/kg/day in males and females, respectively); 2) the reproduction toxicity study was not selected to evaluate dietary exposures for the other registered pyrimidinyl SU chemicals; (3) the chronic oral toxicity study in dogs, which is the study used to establish PODs for sulfometuron methyl, provides similar or lower NOAEL/LOAEL values than the rat reproduction toxicity for all, except 1, SU chemical; and (4) including the proposed new tolerances, dietary risk estimates are <10% of the cPAD using a high-end drinking water exposure value for SUs and there would be no impact on risk estimates calculated for domestic uses.

c. Rat Chronic/Carcinogenicity Study

Two rodent chronic/carcinogenicity studies are required for a food use chemical according to the 40 CFR Part 158 Toxicology Data Requirements. A combined chronic toxicity/oncogenicity and two-generation reproduction toxicity study was previously submitted to the Agency (MRID 42385705), which consisted of a 2-year chronic toxicity/oncogenicity study with a concurrent two-generation reproduction substudy; however, some animals became infected with bronchopneumonia after day 224 requiring quarantine and administration of antibiotic therapy (tetracycline).

Although the registrant has argued that this study should be considered sufficient to fulfill the requirement for a chronic/carcinogenicity study (MRID 50034005), the Agency concluded that the chronic toxicity/oncogenicity portion of the study was compromised and did not satisfy the guideline requirement. The registrant did provide additional analyses in their submission to evaluate tumor findings in female rats excluding females that were also part of the reproduction toxicity study and assessment of overall survival across groups given the bacterial infection. There were no statistically significant or treatment-related increases in tumor findings compared to controls when excluding females from the reproduction toxicity study. There were also no treatment-related effects on survival with survival rates in all groups comparable to historical survival rates for rats of the same strain and age.

An acceptable/guideline mouse carcinogenicity study is available for sulfometuron methyl (MRID 41273602). Mild anemia was observed at the highest dose tested (132 and 183 mg/kg/day in males and females, respectively). There were no adverse effects observed at lower doses. There were no treatment-related increases in tumor incidence compared to controls.

Rat chronic/carcinogenicity studies were used to evaluate chronic dietary exposures for 8 of the other 22 registered SUs (5 pyrimidinyl and 3 triazinyl). For 3 of these, the rat chronic/carcinogenicity studies provided relatively similar NOAEL/LOAEL values as the chronic dog study, which is the study used to establish PODs for sulfometuron methyl. The NOAELs for the rat chronic/carcinogenicity studies of the remaining chemicals were 4-12X lower than the NOAELs for the chronic dog study; however, dose spacing overlapped in several instances.

The majority of the other SU chemicals are classified as not likely to be carcinogenic to humans. There is 1 pyrimidinyl SU chemical classified as suggestive evidence of carcinogenic potential (orthosulfamuron based on thyroid tumors in male rats) and 2 triazinyl SU chemicals classified as Group C - possible human carcinogen (tribenuron methyl based on mammary tumors in rats and triflusulfuron methyl based on testicular tumors in rats). For these 3 chemicals, quantification of cancer risk using a non-linear approach was considered adequate to account for all chronic toxicity, including potential carcinogenicity. Therefore, none of the currently registered SU chemicals have quantitative cancer assessments using a cancer potency factor (i.e., q_1*).

In the last risk assessment (K. Lowe; 15-SEP-2015; D427028), the chronic dietary risk estimates were <10% of the cRfD for all subpopulations using a high-end drinking water exposure value for SUs. With the addition of the tolerances in/on sugarcane commodities, chronic dietary risk estimates are still <10% of the cPAD. As discussed above, non-occupational spray drift and occupational handler and post-application risk estimates were not of concern (i.e., MOEs ≥100). Dermal assessments are also considered conservative since a DAF of 100% was applied to evaluate dermal exposures. Inhalation exposure was assumed to be equivalent to oral exposure. The proposed use for tolerances without U.S. registrations will not result in any changes to the risk estimates calculated for domestic uses.

Based on a weight of evidence (WOE) approach, the HASPOC recommends that the rat chronic/carcinogenicity study is not required for sulfometuron methyl at this time. This

approach was based on the following considerations (1) in the mouse carcinogenicity study, only mild anemia was observed at the highest dose tested and there were no treatment-related increases in tumor incidence compared to controls; 2) the rat chronic/carcinogenicity study was used to evaluate chronic dietary exposures for only 8 of the other SUs, where the chronic dog study yielded similar NOAEL/LOAEL values for 3 of these chemicals; (3) none of the currently registered SU chemicals have quantitative cancer assessments requiring a cancer potency factor; and (4) including the proposed new tolerances, dietary risk estimates are <10% of the cPAD using a high-end drinking water exposure value for SUs and there would be no impact on risk estimates calculated for domestic uses.

IV. HASPOC RECOMMENDATIONS:

The HASPOC, based on a WOE approach, recommends that the rat developmental, reproduction toxicity, and rat chronic/carcinogenicity studies are not required for sulfometuron methyl at this time.